Ex-8

EXHIBIT 8

FDA LETTER
AND
WARNER-LAMBERT RESPONSE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date Rec'd SEP 01 1992
original – CBI
C: R.A. V.P.
Therapeutic Dir.
IND Coord.

AUG 27 1992

NDA 20-130

Parke-Davis (Div. Warner-Lambert Co.)
Attention: Irwin G. Martin, Ph.D.
Director, Worldwide Regulatory Affairs
P.O. Box 1047
Ann Arbor, MI 48106-1047

bcc: W. Merino
Addressee
Central File + orig.
S. Dombey
Sr. Staff - circ.

Dear Dr. Martin:

Reference is made to your new drug application submitted December 27, 1990, pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for the preparation Estrostep-21 (norethindrone acetate and ethinyl estradiol) Tablets and Estrostep-Fe (norethindrone acetate and ethinyl estradiol tablets and ferrous fumarate tablets).

We also acknowledge receipt of your additional correspondence dated February 8, March 28, April 19, 22, and 26, May 16, June 12 and 25, August 22, October 2, 18, and 28, November 7 and 26, and December 20 and 21, 1991; and February 12, March 13, April 16 and 20, May 5, June 11 and 18, 1992.

From May 19 until July 9, 1992, our investigators made an inspection of your establishment at Fajardo, Puerto Rico, with respect to the applicable methods, facilities and controls, and observed a number of important departures from FDA current good manufacturing practice regulations. You were advised at that time of these deficiencies.

Until it is verified in a subsequent inspection that you are operating in compliance with current good manufacturing practice regulations in 21 CFR 210 and 211, we cannot conclude that the methods, facilities, and controls used for the production of the proposed drug preparation(s) are adequate to assure the identity, strength, quality and purity of the product. Consequently, the application is regarded as not approvable under section 505(b)(1) of the Act, and 21 CFR 314.125(b).

In addition to completion of the foregoing requirement, the following changes must be made to the proposed labeling before the application can be approved:

1. The print size of the established name with respect to the proprietary name is too small on the mockups submitted February 8, 1992, of the blister "credit card" labels for Estrostep Fe (trade and institution) and Estrostep 21. These labels should be revised to conform to the requirements at 21 CFR 201.10(g); i.e., the height of the established name must not be less than one-half the height of the tallest letter in the proprietary name.

2. The detailed patient package insert and brief summary must be revised to incorporate the simplified, standardized "**HOW TO TAKE THE PILL (HTTP)**" instructions developed by the Agency with Family Health International (FHI). As a result, the section called INSTRUCTIONS TO PATIENT in your submitted draft will be redundant and must be removed. A labeling guidance for the brief summary and the detailed patient package insert (PPI) is enclosed.

3. The following information regarding sexually transmitted diseases should be added as follows:

a) GENERAL PRECAUTIONS section of the detailed PPI:

"5. Sexually transmitted diseases
The pill does *not* protect against AIDS or any sexually transmitted diseases."

b) BRIEF SUMMARY for the patient, at the end of general information that immediately precedes the "INSTRUCTIONS TO PATIENTS" section (see enclosure):

"The pill does *not* protect against AIDS or any sexually transmitted diseases."

4. The DOSAGE AND ADMINISTRATION section of the Prescribing Information (or Physicians Insert; PI) should not incorporate the HOW TO TAKE THE PILL language verbatim. However, that information should be condensed and rephrased to reflect the information given to the patient.

5. The DESCRIPTION section of the labeling should be revised to include the number of each shape pill and the order in which each shape is to be taken. (This information should also be clearly conveyed to the patient in the brief summary and detailed PPI.)

6. WARNINGS (PI), "d. Dose-related risk of vascular disease from oral contraceptives", second paragraph. The submitted draft is not acceptable. The phrase "and progestin" must be inserted after the following phrases: "Minimizing exposure to estrogen" in the first sentence and "contains the least amount of estrogen" in the second sentence.

7. PRECAUTIONS. In item 10, the submitted draft states, "Pregnancy Category 6". This should be "Pregnancy Category X."

8. Although it is not required at this time, it would be advisable to replace the contraceptive efficacy data from the 1987 Trussell and Kost article with the newer values from Trussell et al. in Studies in Family Planning, 1990.

9. CLINICAL PHARMACOLOGY. A statement acknowledging that the effect of food and the effect of morning versus evening administration on the pharmacokinetics of Estrostep is unknown should be added to this section.

We note that in your letter dated April 16, 1992, you made commitments regarding the following Phase 4 actions:

1. You agreed to conduct a multiple dose biopharmaceutics study designed to address the deficiencies discussed with the Division of Biopharmaceutics on several occasions. You also agreed to submit the protocol within 30 days after approval. (We request that the study be completed within one year following your receipt of the Agency's comments on the protocol.) The study will use the marketed tablets and will incorporate dosing regimens of the product consistent with its labeling.

2. You also agreed to update the CLINICAL PHARMACOLOGY section of the labeling using data from the above study (bioavailability and pharmacokinetics values) and other relevant information (metabolism and excretion) will be included at that time.

Our review of this application has been completed, and no additional deficiencies have been identified.

Within 10 days after the date of this letter, you are required to amend the application or notify us of your intent to file an amendment or follow one of the other options under 21 CFR 314.120. In the absence of such action FDA may take action to withdraw the application. Any amendment should respond to all the deficiencies listed. A partial reply (one which does not address all remaining outstanding deficiencies) will not be processed as a major amendment, nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, please contact Ms. Enid Galliers at 301-443-3510.

Sincerely yours,

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research

ENCLOSURE

DISTRIBUTION
I. Martin
W. Merino
O. Richards
M. Taylor
CBI File
R.A. AA NDA 20-130 File

September 3, 1992

NDA 20-130
Estrostep®
Ref. No. 26

Re: General Correspondence

Solomon Sobel, M.D.
Director
Division of Metabolism and Endocrine
Drug Products (HFD-510)
Document Control Room 14B-03
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Sobel:

Reference is made to our New Drug Application (NDA 20-130) for Estrostep® (norethindrone acetate and ethinyl estradiol, USP) Tablets for oral contraception submitted on December 27, 1990.

Additional reference is made to your letter of August 27, 1992 that stated the application is not approvable under Section 505(b)(1) of the Act and 21 CFR 314.125(b). Reference is also made to a telephone conversation between Ms. E. Galliers and I on August 25, 1992 regarding review of the proposed labeling and response to your then proposed August 27, 1992 letter.

In accordance with your letter and as detailed in 21 CFR 314.120(a), we are notifying you of our intent to amend this application.

Should you have any questions regarding this submission, please feel free to call me at 313/996-5000 or FAX 313/996-7890.

Sincerely,

Mary E. Taylor
Senior Manager
Worldwide Regulatory Affairs

MT/rt/9192.26